REMARKS

Support for new Claim 47 can be found at page 13, lines 16 *et seq* of the present specification. The amendments to Claim 43-44 are minor and editorial in nature. Hence, new Claim 47 and the amendments to Claims 43-44 do not constitute new matter, and thus entry is requested.

In paragraph 1 on page 2 of the Office Action, the Examiner states that the Second Supplemental Information Disclosure Statement filed February 7, 2002, is not of record. Further, the Examiner states that if Applicants wish to make of record U.S. Patent Publication 2002/00022717, they must do so in accordance with 37 C.F.R. § 1.97.

Accordingly, Applicants submit herewith a copy of said Second Supplemental Information Disclosure Statement, along with a copy of the filing receipt showing that the U.S. Patent and Trademark Office received this document on February 7, 2002.

In addition, Applicants do not believe that submission of U.S. Patent Publication 2002/00022717 is necessary, since such is cumulative of U.S. Patent Publication 2002/0002273, which is cited in the Second Supplemental Information Disclosure Statement. Nonetheless, to complete the record, Applicants file herewith Form PTO/SB/08 A&B (modified) with respect to U.S. Patent Publication 2002/00022717.

The Examiner is requested to note that U.S. Serial No. 09/585,743, filed June 2, 2000, i.e., the parent of U.S. Patent Publication 2002/0002273 is believed to be pending and may also be relevant to the present application.

In paragraph 5 on page 1 of the Office Action, the Examiner indicates that Claims 33-40 and 42-46 have been allowed. However, in paragraph 6 on page 1 of the Office Action, the Examiner indicates that Claim 41 is still rejected.

In particular, in paragraph 4 on page 2 of the Office Action, the Examiner rejects Claim 41 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner states that Claim 41 is directed to a monoclonal antibody, produced using any immunogen, which has specificity for the same antigen recognized by the monoclonal antibody produced by hybridoma RAP-42-OVAF2#1hc. However, the Examiner states that the specification only provides enablement for the production of monoclonal antibodies using the specific 31 and 42 rapamycin immunogens disclosed therein.

Furthermore, the Examiner states that the Molnar-Kimber and Bycroft Declarations teach that there was no reasonable expectation at the time the invention was made, given the immunosuppressive nature of rapamycin and its mode of action in the body, which differs from that of FK-506, that one could successfully obtain monoclonal antibodies specific for a rapamycin. The Examiner goes on to state that Applicants' invention lies in determining which specific rapamycin-carrier conjugate will provide rapamycin specific antibodies.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, Applicants respectfully submit that the Examiner has confused the standard for enablement with the standard for

obviousness. The standard for enablement is whether it would require "undue experimentation" to practice the scope of the invention as claimed, whereas the standard for obviousness is whether, in light of the prior art, there was a "reasonable expectation of success".

The Bycroft and Molnar-Kimber Declarations were submitted to rebut the Examiner's obviousness rejection, not an enablement rejection. Further, contrary to the Examiner's apparent contention, the Bycroft and Molnar-Kimber Declarations do not focus on the specific immunogen employed in order to overcome the prior art rejection. That is, contrary to the Examiner's contention, Applicants' invention does not lie in determining which specific rapamycin-carrier conjugate will provide rapamycin specific antibodies. Rather, as discussed therein, and in the Amendment filed February 7, 2002, Applicants' invention lies in the discovery that one could successfully make antibodies specific to rapamycins at all.

In particular, the present invention is unobvious over the prior art, since at the time of the present invention, in April of 1993, there was no reasonable expectation that one could successfully obtain monoclonal antibodies to rapamycins, even in view of the teachings of the prior art, because (a) the general understanding that molecules possessing regions of conformational flexibility (such as the rapamycin macrolide molecules) are less likely to be recognized by B cells, and therefore less likely to generate monoclonal antibodies; (b) the generation of monoclonal antibodies to potent immunosuppressive agents (such as rapamycins) was known to be difficult and

unpredictable; (c) although monoclonal antibodies had been generated (with some difficulty) to the prior art compound FK-506, there are substantial structural differences between rapamycins and FK-506, and rapamycins exhibit significantly different biological activities to FK-506 both at the cellular and the molecular level; (d) no monoclonal antibodies had been generated to an immunosuppressant that has the same mode of action as rapamycins at the cellular level, i.e., (i) blocks the proliferative response of T cells to the IL-2 signal and the T helper effect on B cells, and (ii) suppresses B cell activation and antibody production; and (e) no monoclonal antibodies had been generated to an immunosuppressant that have the same mode of action as rapamycins at the molecular level, i.e., bind to FKBP and then to a target, later identified as mTOR/FRAP/RAFT1.

Moreover, the present specification clearly teaches that antibodies to rapamycins can be obtained using a conjugate other than one at positions 31 and 42, i.e., the specification teaches that conjugates at the position 27 can be used to obtain the rapamycin-specific monoclonal antibodies (see page 8, lines 5 *et seq* and page 12, lines 19 *et seq* of the present specification).

Thus, Applicants respectfully submit that the present specification is clearly enabling for obtaining the monoclonal antibodies of the present invention, and it should not be necessary to recite in Claim 41 the immunogen used to obtain the claimed monoclonal antibodies.

In further support of Applicants' position, the Examiner is directed to the Response After Final filed August 1, 2002, wherein U.S. Patent 5,474,771, issued to Lederman et al, was discussed. As noted therein, the Lederman Patent contains claims similar to Claim 41. In particular, Claim 1 of the Lederman Patent is as follows:

> Claim 1. A monoclonal antibody which specifically binds and forms a complex with the 5c8 antigen located on the surface of activated T cells and thereby inhibits T cell activation of B cells, the 5c8 antigen being an antigen to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) specifically binds.

Lederman discloses that the deposited 5c8 antibody was obtained using D1.1 cells as the immunogen (see col. 15, lines 18 *et seq*). However, it should be noted that Claim 1 of the Lederman Patent is not limited in terms of the immunogen used to obtain the deposited 5c8 antibody. Thus, by analogy, Claim 41 of the present application also need not be limited in terms of the immunogen used to obtain the claimed monoclonal antibody, contrary to the Examiner's contention.

Applicants respectfully submit that the Examiner is improperly asking Applicants to change product Claim 41 into a product-by-process claim. Product-by-process claims may be used to meet the requirements of 35 U.S.C. 112, second paragraph. They are not used to meet the enablement requirement of 35 U.S.C. § 112, first paragraph. As discussed above, there is no question that the present specification enables how to make the antibodies of Claim 41, nor is there any question that the claimed antibody is particularly and distinctly recited in

Claim 41. Thus, Applicants respectfully submit that the Examiner's rejection is legally improper.[1/]

Accordingly, Applicants respectfully submit that Claim 41 is enabled by the present specification, and thus request withdrawal of the Examiner's rejection.

In view of the amendments to Claims 43-44, the addition of new Claim 47 and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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[1/] The Examiner is requested to note that it is clearly proper for an application to contain both product and product-by-process claims (*In re Hughes*, 182 USPQ 106 (CCPA 1974)).

A P P E N D I X

Marked-Up Version of Changes

IN THE CLAIMS:

The claims are amended as follows:

Claim 43. (Amended) A hybridoma [capable of producing] which produces a monoclonal antibody as defined in any one of Claims 33, 34, 35, 36, 37, 38 or 41.

Claim 44. (Amended) A hybridoma [capable of producing] which produces a monoclonal antibody as defined in Claim 42.

New Claim 47 is being added.